

# Food allergy and anaphylaxis

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**Abstract:** Anaphylaxis is a severe and potentially life-threatening allergic reaction. There are numerous potential causes, with food allergy being the leading cause in children and the focus of this review. Most reactions involve an IgE-mediated mechanism, although non-IgE-mediated and nonimmunologic reactions can occur. Various cofactors to be discussed can place certain individuals at an increased risk of severe or fatal anaphylaxis. The clinical manifestations of anaphylaxis are broad and may involve multiple body systems. Diagnosis of food-related anaphylaxis is primarily based on signs and symptoms and supported, wherever possible, by identification and confirmation of a culprit food allergen. First-line treatment of anaphylaxis is intramuscular administration of epinephrine. Long-term management is generally focused on strict allergen avoidance and more recently on food desensitization using immunotherapy. This review provides an overview of anaphylaxis with a specific focus on food allergy.

**Keywords:** allergic reaction, food, trigger, epinephrine, avoidance, immunotherapy

## Introduction

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death.<sup>1</sup> Although human studies of the immunologic mechanisms of anaphylaxis are limited, most cases involve the interaction between an allergen and allergen-specific IgE bound to high-affinity IgE receptors on mast cells and basophils. The most common causes of IgE-dependent reactions include food, medications, Hymenoptera venom, and latex rubber.<sup>2</sup>

Although less common, anaphylaxis can also involve non-IgE-mediated mechanisms, including IgG- and complement-mediated reactions, and direct mast cell and basophil activation in the absence of immunoglobulins. Potential causes include physical factors, such as exercise, cold and heat, and iatrogenic agents, including radiocontrast media and opiates. Regardless of the underlying mechanism or trigger, ultimately, there is activation of a signaling cascade resulting in mast cell and basophil degranulation. These cells release multiple mediators including histamine, tryptase, leukotrienes and prostaglandins, which lead to the clinical manifestations of anaphylaxis. Cytokines important in allergic disease, including TNF- $\alpha$ , IL-4, IL-5, IL-6, IL-10, and IL-13, activate complement and the kallikrein-kinin systems, further contributing to symptoms. Platelet-activating factor (PAF) and nitric oxide also appear to play a role. PAF is released during allergic reactions, and decreased activity of PAF acetylhydrolase, the enzyme that degrades PAF, has been associated with more severe anaphylaxis.<sup>2</sup> Non-IgE-mediated reactions are clinically indistinguishable and have similar acute

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management despite their underlying mechanism.<sup>3</sup> The objective of this paper is to review recently published evidence related to food allergy/anaphylaxis addressing prevalence, diagnostics, and treatment, including primary prevention and immunotherapy, in the past year (January 1, 2017, to January 4, 2018).

## Methods

A database search (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE, and Versions(R) for articles, between January 1, 2017, and January 4, 2018) was conducted using the following key words: “anaphylaxis”, AND-ed “food allergy”.

## Eligibility criteria

The following eligibility criteria were used for article inclusion: population: patients with food allergy and/or at risk for anaphylaxis; intervention: any approaches or protocols that incorporated a strategy for food allergy and anaphylaxis management; comparator: any studies irrespective of whether there was a comparator included in the study design; outcomes: any related to prevalence, diagnostics, and treatments including primary prevention and immunotherapy; and study design: experimental studies (e.g., randomized controlled trials [RCTs]), other experimental designs (e.g., non-randomized methods of assignment, controlled before–after studies, and interrupted time series), and observational studies (e.g., prospective or retrospective cohort, cross-sectional, and case–control). We excluded case reports, opinion-based reports (i.e., editorials, letters, and non-systematic or narrative reviews), and basic science or animal (nonhuman) studies.

## Data synthesis

The analysis involved summarizing the data and presenting the results in a narrative synthesis. We prepared descriptive tables to give an overview of the included study characteristics. This manuscript was not designed to perform quantitative analysis, meta-analysis, or assessment of risk of bias.

Of 304 potentially relevant articles, a total of 15 articles with new insights on food allergy/anaphylaxis were selected. The majority of the studies (Table 1) consisted of retrospective studies (n=7), population-based cohort studies (n=2), clinical trials (n=3), cross-sectional surveys (n=1), prospective studies (n=1), and retrospective chart review (n=1).

The studies in the following overview address new insights on food allergy/anaphylaxis addressing prevalence,

diagnostics, acute management, as well as primary prevention and immunotherapy (oral, epicutaneous, and sublingual routes).

## Prevalence and characterization of food allergy/anaphylaxis

Increasing prevalence of anaphylaxis is supported by a recent US study conducted between January 1, 2001, and December 31, 2010, which examined records of 2,386 Olmsted County, MN, residents with a diagnosis of anaphylactic shock or related diagnoses (e.g., venom-related toxic events, medication reactions). A total of 631 cases that fit the clinical criteria of anaphylaxis were identified (median age 31 years). The overall incidence of anaphylaxis was 42/100,000 person-years. There was an increase in the overall incidence of anaphylaxis during the study period, with an average increase of 4.3%/year ( $P<0.001$ ). A 9.8%/year increase in the incidence of food-related anaphylaxis was also noted.<sup>4</sup>

Previous studies have reported food as the most common cause of anaphylaxis, which account for 30% of fatalities.<sup>5</sup> Our review included a recent retrospective study of 4,777 electronic records (July 2002 to October 2013), which revealed that 730 (15%) patients evaluated in the Allergy and Immunology Department of Cleveland Clinic (median age 34 years; 73% adults, 59% females, 87% Caucasians) met the World Health Organization (WHO) definition of anaphylaxis. The top three causes were food (29.9%), venom (26.4%), and medications (13.3%), with venom being the most common in adults.<sup>6</sup> In children, the most common foods were peanuts (32.0%), tree nuts (22.7%), milk (17.2%), and eggs (16.4%) as compared to adults where the most common foods were shellfish (34.4%), tree nuts (20.0%), and peanuts (12.2%).<sup>6</sup>

In addition, a Canadian study (between April 2011 and February 2014) prospectively examined recurrence rates of anaphylaxis among 292 children (mean age 6.5 years) who attended an emergency department with anaphylaxis (two tertiary care pediatric hospitals and a third general hospital). The study reported an annual recurrence rate of 17.6% with food being the most common cause of these recurrences (84.6%).<sup>10</sup>

A Canadian survey of self-reported food allergy showed an estimated food allergy prevalence of 6.9% in children (1–17 years) and 7.7% in adults (18+ years).<sup>7</sup> Approximately 1.1% of respondents were allergic to peanut (PN). These estimates are higher than a recent electronic health record (Partners HealthCare, Boston, MA, USA) review that reported a 3.6% prevalence of food allergy (97,482 of 2,714,851 patients).<sup>8</sup>

**Table I** Summary of included studies

Theme	Study	Objective	Setting/duration	Population	Design
Prevalence	Gonzalez-Estrada et al <sup>6</sup>	To determine the pattern of anaphylaxis at a tertiary care referral center	Allergy and Immunology Clinic, Cleveland, OH, USA Electronic medical record review between 2002 and 2013	N=730 patients with anaphylaxis	Retrospective study
	Acker et al <sup>8</sup>	To determine the prevalence of food allergy and intolerance documented in the electronic health records (EHR) allergy module	Allergy data review with large health care organization's EHR (Partners Healthcare, Boston, MA, USA) between 2000 and 2013	N=97,482 patients with one or more food allergies or intolerances	Retrospective study
	Leickly et al <sup>9</sup>	To confirm new observations on peanut allergy and answer current concerns that families and health care providers have about peanut allergy	Riley Peanut Registry; Riley Outpatient Center in Indianapolis; Indiana University North in Carmel, IN, USA; and Riley Children's Specialists in Bloomington, IN, USA, between April 2011 and March 2016	N=1,070 children with peanut allergy	Retrospective study
	Lee et al <sup>4</sup>	To determine the incidence rate and causes of anaphylaxis during a 10-year period in Olmsted County, MN, USA	Rochester Epidemiology Project, Olmsted County, MN, USA, from 2001 to 2010	N=631 cases of anaphylaxis	Population-based incidence study
	O'Keefe et al <sup>10</sup>	To determine the recurrence rate of anaphylaxis in children medically attended in an emergency department (ED)	EDs, Outaouais region of Quebec, Canada, between April 2011 and February 2014	N=292 children with anaphylaxis	Prospective cohort study
Diagnostics	Griffiths et al <sup>18</sup>	To review currently available diagnostic tests performance, how they are used, and how their use might be optimized to address unmet needs in allergy diagnosis	National Allergy Service for Wales at the University Hospital of Wales between April 2011 and March 2014	N=1,434 females and 634 male patients; new referrals with clinical histories and presented with diagnostic difficulty	Retrospective study
	Akuete et al <sup>22</sup>	To examine the epidemiology, symptoms, and treatment of clinical low-risk oral food challenges (OFCs) in the non-research setting	Data from five US food allergy centers: Texas Children's Hospital Food Allergy Program (South); University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center (North Midwest); Riley Hospital for Children at Indiana University Health (Midwest); University of Washington School of Medicine, Northwest Asthma & Allergy Center (Northwest); and Boston Children's Hospital (Northeast); study conducted from January 1, 2008, to December 31, 2013	N=6,377 open OFCs	Retrospective study
	Chan et al <sup>23</sup>	To compare reaction profiles from food challenges and parent-reported reactions on accidental ingestion and assess predictors of severe reactions	HealthNuts study; birth cohort 2006–2009; Specialist Clinic at Melbourne's Royal Children's Hospital	2-month-old infants via their parents/guardians at childhood immunization sessions across the city of Melbourne, Australia N=5,276 12-month-old infants	Longitudinal population-based cohort study
	Yanagida et al <sup>24</sup>	To identify the risk factors for severe symptoms during OFC testing among high-risk patients	Sagamihara National Hospital, Japan Between June 2008 and June 2012	N=393 patients ≥5 years old with anaphylactic history	Retrospective chart review

(Continued)

**Table 1** (Continued)

Theme	Study	Objective	Setting/duration	Population	Design
Acute management	Cantrell et al <sup>30</sup>	To determine whether EpiPens expired up to 50 months retain their stated potency	Two-week period; patients and practitioners at a community clinic were asked to provide unused, expired EpiPens	N=40 expired EpiPens	Retrospective study
	Feuille et al <sup>33</sup>	To assess time trends in food allergy diagnoses, epinephrine autoinjector (EAI) prescriptions, and EAI administrations in the school setting	Student data from the New York City Department of Health and Mental Hygiene, between school years 2007 and 2013 pertaining to diagnoses of food allergy, student-specific EAI orders, and EAI administrations among students in New York City	N=6,418,039 students	Retrospective study
	Waserman <sup>34</sup>	To examine the availability of EAIs globally	Online survey administered to patients (with food allergy) through a global network (48 countries) of patient allergy associations (August–December 2016)	N=7,241 patients with food allergy	Cross-sectional study
Oral immunotherapy (OIT)	Vickery et al <sup>39</sup>	To test the safety, effectiveness, and feasibility of early OIT (E-OIT) in the treatment of peanut allergy	University of North Carolina, at Chapel Hill, Chapel Hill, NC, USA	N=40 children aged 9–36 months with suspected or known peanut allergy	Clinical trial (single center)
Epicutaneous immunotherapy (EPIT)	Jones et al <sup>41</sup>	To evaluate the clinical safety and immunologic effects of EPIT for the treatment of peanut allergy	Five clinical Consortium of Food Allergy Research (CoFAR) sites; 52 weeks of blinded treatment	N=74 peanut allergy Aged 4–25 years Placebo (n=25) Viaskin® Peanut (VP) 100 µg (n=24) VP 250 µg (n=25)	Multicenter, double-blind, randomized, placebo-controlled study
	Shreffler <sup>42</sup>	To assess the long-term efficacy and safety of VP treatment up to 36 months	24-month extension of the VIPES Phase IIb randomized controlled trial (RCT) was conducted Subjects rolled over into the open-label OLFUS-VIPES extension with VP 250 µg	N=171 subjects (6–55 years)	Open-label extension study

Allergic comorbid diseases have also been examined and are more prevalent in food allergic individuals. A US registry of PN allergic children (The Riley PN Registry), which reported the 5-year experience of 1,070 children (mean age 1 year), showed coexistent atopic dermatitis (65%), asthma (41%), and additional food allergies (68.7%).<sup>9</sup>

## Risk factors for anaphylaxis

Although our review did not capture recent studies examining this question, previous studies<sup>3,11–13</sup> have shown that patient factors can increase the risk of severe or fatal anaphylaxis.

Examples of age-related factors include anaphylaxis in infancy, which is difficult to recognize as they cannot describe their symptoms, and risk-taking behaviors in teens and young adults including failure to avoid known triggers and carry an epinephrine autoinjector (EAI). In adults, chronic diseases such as asthma and cardiovascular diseases and their

treatments with beta-blockers and angiotensin-converting enzyme inhibitors place them at an increased risk.<sup>3</sup> Beta-blockers can increase reaction severity and specifically can make anaphylaxis more difficult to treat.<sup>3</sup>

Mast cell disorders, including mastocytosis, and severe atopic diseases, including allergic rhinitis, can also increase the risk of severe or fatal anaphylaxis. Cofactors (external circumstances associated with more severe allergic symptoms) such as exercise, alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), acute infection, stress, and perimenstrual status can decrease allergen thresholds and amplify an anaphylactic reaction.<sup>11,12</sup>

Factors that have been associated with fatality with regard to food-induced anaphylaxis include reactions to PN and tree nut (TN), delayed administration of epinephrine, a previous history of food allergy, asthma especially if poorly controlled, and age (more frequent in teenagers and young adults).<sup>13</sup>

## Diagnosis and clinical manifestations

The definition of anaphylaxis is based on an expert consensus and was published in 2006. Anaphylaxis is highly likely when any one of these three criteria are fulfilled: 1) sudden onset of an illness, with involvement of the skin, mucosal tissue, or both and at least one of respiratory compromise or reduced blood pressure or associated symptoms of end-organ dysfunction; 2) two or more of the following that occur rapidly after exposure to a likely allergen: skin/mucosal involvement, respiratory compromise, reduced blood pressure, or gastrointestinal (GI) symptoms; and 3) reduced blood pressure after exposure to a known allergen.<sup>3</sup>

Cutaneous manifestations are reported in 80%–90% of all patients. In the Riley PN Registry, most reactions involved the skin (55%).<sup>9</sup> In the absence of skin symptoms, anaphylaxis may be difficult to recognize and can occur in up to 20% of patients, specifically food or venom allergy.<sup>1,3</sup> Anaphylaxis can range in severity from mild symptoms to very severe reactions, progressing within minutes to respiratory compromise or cardiovascular collapse and death. It is important to recognize that the clinical manifestations and severity of reactions are unpredictable and may differ from one patient to another and from one episode to another in the same patient.<sup>3</sup>

Biphasic reactions can also occur, where patients experience a recurrence of symptoms within 72 hours of the initial anaphylactic event without re-exposure to the trigger. In a meta-analysis by Lee et al,<sup>14</sup> the reported rate of biphasic reactions among the included studies was 4.6%. They noted that the risk of a biphasic reaction was greater with hypotension on presentation and an unknown inciting trigger. In general, it is recommended that all patients be observed for at least 4–6 hours after an anaphylactic reaction; however, this should be individually tailored.<sup>14</sup>

## Diagnostics

Laboratory studies may help establish a diagnosis of anaphylaxis. Increased levels of serum total tryptase and plasma histamine can be observed during or shortly after an acute anaphylactic episode. Tryptase levels peak 60–90 minutes after the onset of symptoms and remain elevated for at least 5 hours, whereas plasma histamine remains elevated for only 30–60 minutes.<sup>15</sup> Normal levels do not rule out anaphylaxis and are usually present in patients with anaphylaxis to food and in those who are normotensive.<sup>16</sup>

## Skin prick tests (SPTs)

To identify a potential trigger (e.g., food, medications, insect stings), SPT is a reliable method.<sup>17</sup> With regard to food allergy, a positive SPT has a sensitivity of ~90% and a specificity of ~50%. An SPT alone is not sufficient for diagnosis and must be interpreted in the context of the clinical history. The negative predictive value (NPV) of SPT is >95%, and a negative result essentially confirms the absence of IgE-mediated allergic reactivity.<sup>13</sup>

## Serum-specific IgE

A serum-specific IgE can be a useful alternative if an SPT cannot be performed or is unavailable. The ImmunoCAP method uses a fluorescent enzyme immunoassay to detect selective specific IgE antibodies. This is in contrast to Immuno Solid-phase Allergen Chip (ISAC) that measures specific IgE antibodies against multiple allergen components in a single assay.<sup>18</sup> Higher concentrations of food-specific IgE levels correlate with an increasing likelihood of a clinical reaction but do not correlate well with reaction severity. In food-sensitized patients, specific IgE levels with >95% predictive risk values of a positive (failed) food challenge have been identified. The 95% positive predictive value (PPV) calculations depend on the population sampled and vary with specific prevalence rates in different geographic regions; hence, they are not completely generalizable. These levels are established for cow's milk (CM) ( $\geq 15$  kU/L), egg ( $\geq 7$  kU/L), PN ( $\geq 14$  kU/L), TN ( $\geq 15$  kU/L), and fish ( $\geq 20$  kU/L).<sup>13</sup>

Our review yielded a retrospective study of 2,068 new patient (69% female) referrals between April 4, 2011, and March 31, 2014, at the University Hospital of Wales, which revealed that in patients with nut allergy, the detection rates of SPT (56%) and ISAC (65%) were lower than those of ImmunoCAP (71%). In addition, ISAC had a higher detection rate (88%) than ImmunoCAP (69%) or SPT (33%) for the diagnosis of oral allergy syndrome (OAS). The higher detection rate of OAS was explained as being due to the lack of availability of component-resolved diagnostics (CRDs) in SPT, in particular pathogenesis-related (PR)-10. In this population, they concluded that although ImmunoCAP, ISAC, and SPT performed similarly for confirmation of food allergy and anaphylaxis, the ISAC was the most useful for confirmation of OAS.<sup>18</sup>

## CRD testing

CRD testing may predict the risk or severity of allergic reactions to specific food by measuring IgE to specific components and epitopes within an allergen source.<sup>19</sup> PN component

testing studies have shown that positive testing to the peanut component Ara h2 is more sensitive and specific than IgE to whole PN and the most consistent marker for predicting PN allergy. Serum IgE to Ara h2 has 60%–100% sensitivity and 60%–90% specificity in predicting reactivity.<sup>20</sup> CRD testing can also identify cross-reactive specific components to other similar allergens from different pollen species or food items. For example, the PN component Ara h8 is positive in patients experiencing OAS.<sup>21</sup>

## Oral food challenges (OFCs)

If diagnostic tests remain unclear, an OFC may be considered for a suspected food and involves gradual feeding of the food to assess clinical reactivity.<sup>13</sup> Although uncommon, recent studies report the rate of anaphylaxis during OFC to range from 2% to 3%.<sup>22,23</sup> A Japanese retrospective study evaluated 393 patients (median age 8.3 years;  $\geq 5$  years old), defined as of high risk of a severe reaction [anaphylactic history or antigen-specific IgE ( $>30$  kU/L) to egg, milk, wheat, or peanut], and observed anaphylaxis (WHO definition) in 48% of cases during in-hospital OFC. Risk factors that were associated with severe symptoms were a history of a previous anaphylactic reaction and older age.<sup>24</sup> This underscores the recommendation that OFCs must be conducted cautiously by trained health care providers, where resuscitation equipment is available, and anaphylaxis can be appropriately managed.<sup>19</sup>

## Acute management

Acute management of an IgE-mediated anaphylactic reaction starts with rapid assessment of airway, breathing, and circulation. First-line treatment is epinephrine administered intramuscularly into the lateral thigh.<sup>25</sup> Treatment should be provided even if the diagnosis is uncertain since there are no absolute contraindications to the use of epinephrine.

The dose of epinephrine for the acute treatment of anaphylaxis is 0.01 mg/kg up to a maximum of 0.5 mg every 5–20 minutes as necessary. Glucagon should be considered in patients on beta-blockers.<sup>15</sup> All individuals receiving emergency epinephrine must be transported to hospital immediately for evaluation and observation.

EAI devices are available in two dosages (0.15 and 0.3 mg) and prescribed according to weight. The 0.3 mg dosage is indicated for individuals  $\geq 30$  kg and 0.15 mg dosage for those 15–30 kg.<sup>26,27</sup> Both the American Academy of Pediatrics and Canadian Pediatric Society recommend switching most children from 0.15 to 0.30 mg when they reach a body weight of  $>25$  kg.<sup>28,29</sup>

EAI devices should be stored avoiding temperature extremes and replaced before the expiration date. In a recent study of EpiPens, it was shown that although there was a gradual decline in concentration over time,  $>80\%$  of their labeled concentration was retained 50 months after the expiration dates. The authors concluded that the expired EpiPens would likely still provide a beneficial pharmacologic response.<sup>30</sup>

A significant number of states and Canadian provinces have allowed schools to stock EAI devices and train school staff on when to use and how to use EAI devices.<sup>31,32</sup> In a retrospective study of students ( $n=6,418,039$ ) attending New York City district public schools, a total of 337 EAI administrations were reported between 2008 and 2013, highlighting an increasing incidence of 1.3 EAI administrations per year (from 3.7/100,000 students in 2008–2009 to 10.1/100,000 students in 2012–2013). A total of 42% of students were administered an EAI due to food-related anaphylaxis (84% PN allergy), and 58% of students treated for anaphylaxis were without a documented allergy. Treatment in these schools most commonly (52%) relied on stock supply of nonstudent-specific EAI devices.<sup>33</sup> The most frequent cause of anaphylaxis in this study was found to be food. This emphasizes the importance of stock epinephrine in the management of anaphylaxis in the school setting and potentially in other high traffic public places.

The proportion of total students who provided documentation of physician-diagnosed food allergy increased significantly from 0.39% in 2007–2008 to 1.43% in 2012–2013 ( $P<0.001$ ), as did the proportion of total students with a physician-prescribed EAI, which also increased significantly over the years of the study from 0.26% in 2007–2008 to 0.74% in 2012–2013 ( $P<0.001$ ).<sup>33</sup>

Recent findings from a global survey on food allergy revealed that 29% of respondents experienced an allergic reaction but did not administer an EAI for reasons ranging from not thinking the reaction was severe enough to fear of using it.<sup>34</sup> This emphasizes the importance of educating patients and their caregivers on avoidance strategies, taking into consideration relevant triggers, age, activity, occupation, hobbies, residential conditions, access to medical care, patient's anxiety, and the appropriate use of EAI devices. All patients at risk of anaphylaxis must always carry an EAI and wear medical identification (i.e., MedicAlert bracelet/necklace).<sup>35</sup> An anaphylaxis action plan outlining the recognition and treatment of an anaphylactic reaction as well as the trigger allergen should be developed and made available to the appropriate people (e.g., caregivers, daycare providers, teachers, employers).

Since food avoidance still plays a significant role in food allergy management, a well-balanced elimination diet will keep an individual free of symptoms while maintaining nutritional status. An exception to strict avoidance is CM and egg allergy. Previous studies have shown that the majority of CM-allergic (74%) and egg-allergic (71%) children can tolerate baked milk and baked egg, respectively, which increases the rate of oral tolerance to these food items.<sup>36,37</sup>

## Immunotherapy and desensitization

Food allergy research as well as recent media attention has focused on food desensitization using immunotherapy as a means of food allergy treatment. With immunotherapy, the aim is to first achieve desensitization (temporary) with the ultimate goal being tolerance (permanent) to the allergen. Oral, epicutaneous, and sublingual routes of food desensitization administration have continued to be examined as potential treatments and are primarily available through research protocols as there are currently no approved products for desensitization in the USA and Canada.

### Oral immunotherapy (OIT)

In most OIT protocols, food is gradually introduced under medical supervision, with increases in the food dose occurring every 2 weeks. This is continued until a predefined maintenance dose is reached, which is then continued for months to years to maintain desensitization. With the exception of the biweekly dose escalations, daily dosing is done at home. Efficacy is determined by an OFC to the food in question. While multiple randomized control trials have confirmed that OIT is often effective for inducing desensitization (temporary unresponsiveness) and increasing thresholds to various food allergens, tolerance (sustained unresponsiveness) has not generally been achieved. The rate of successful desensitization reported in studies ranges from 35% to 100% (intention to treat) and varies based on the patient's age, food, chosen food dose, differences in OIT protocols used, and which outcomes were measured (e.g., primary outcome on OFC).<sup>38</sup> In a randomized, placebo-controlled trial, Vickery et al<sup>39</sup> investigated the efficacy of peanut OIT in young children aged 9–36 months using a low-dose (300 mg/day peanut protein) and high-dose (3,000 mg/day) OIT. They demonstrated that overall 78% of patients achieved sustained unresponsiveness (defined as the ability to consume 5 g of peanut protein without dose-limiting symptoms during an exit double-blind, placebo-controlled food challenge [DBPCFC]) to peanut 4 weeks after stopping OIT and reintroduced peanut into the diet.<sup>39</sup> Although this is the highest rate reported to date,

patients should be aware that this is still not synonymous with cure, given the short duration of follow-up. Study authors suggest that allergic responses may be more easily modified in young children, but ongoing studies are required to strengthen this hypothesis. There were no treatment-related, severe adverse events (AEs), hospitalizations, or deaths. A total of 85% of the subjects experienced AEs (rash, skin, sneezing/congestion, hives, rash, GI symptoms) that resolved without treatment or with oral antihistamines only (47%). A total of 10 subjects withdrew from the study due to AEs. Epinephrine was not administered during dose-escalation visits but was used once at home dosing.

It has also been observed that cofactors (exercise, infection, etc.) can influence the risk of acute AEs with oral food desensitization, an important consideration in ensuring safety and efficacy when carrying out such therapies.<sup>38</sup> OIT studies have reported improved quality of life and less anxiety for those who have completed this process.<sup>38</sup>

There are currently no approved OIT therapies; however, recent findings of the Peanut AR101 (Aimmune Therapeutics, Brisbane CA, USA) Phase II clinical trial of 55 peanut allergic subjects (4–26 years old) concluded that AR101 (n=29) significantly reduced symptom severity during exit DBPCFCs and modulated peanut-specific cellular and humoral immune responses versus placebo (n=26). GI symptoms were the most common treatment-related AEs, with six AR101 subjects withdrawing (patient dose ranged between 6 and 80 mg during the escalation phase), four subjects due to recurrent GI AEs.<sup>40</sup>

### Epicutaneous immunotherapy

In epicutaneous immunotherapy, the food is contained in a patch, which is applied to the skin. A randomized double-blind, placebo controlled trial compared two doses of Viaskin Peanut 100 µg (n=24) and Viaskin Peanut 25 µg (n=25) versus placebo (n=25) in children and young adults with peanut allergy (aged 4–25 years; physician-diagnosed peanut allergy or convincing clinical history of peanut allergy, positive SPT wheal size ≥3 mm, or peanut-specific IgE level >0.35). The primary end point was the proportion of participants with a successful outcome after 52 weeks of blinded treatment. Treatment success was defined as either passing a double-blind, placebo-controlled OFC with 5,044 mg of peanut protein at week 52 or by a 10-fold or greater increase in the successfully consumed dose (SCD) of peanut protein compared with the baseline OFC. The results revealed that treatment success was achieved in 12% of placebo-treated participants, 46% of VP100 participants ( $P=0.005$ ), and 48%

of VP250 participants ( $P=0.003$ ). It was also noted that the highest responses were in children 11 years old or younger.<sup>41</sup> In the extension study that included 18 children (6–11 years) treated with 250 µg PN patches for 3 years, there was a trend toward better treatment responses (83.3%) with long-term therapy.<sup>42</sup> The adherence rate in these studies was observed to be >95%. In addition, no serious AEs or epinephrine use was reported. Most AEs were mild to moderate, related to the application site, and decreased in both severity and frequency over time.

## Sublingual immunotherapy (SLIT)

Desensitization by SLIT utilizes dissolvable tablets or liquid allergen extracts that are placed under the tongue daily. SLIT uses lower doses than OIT and is associated with less AEs, but is generally not as effective.<sup>38</sup>

## Food allergy prevention

### Early introduction of food

There have been a number of studies centered on food allergy prevention. Infants with a first-degree relative with a history of allergic disease (allergic rhinitis, asthma, eczema, or food allergy) is at a greater risk of developing food allergy.<sup>43</sup>

A number of observational studies have suggested that the early and regular consumption of PN, egg, or CM may prevent the development of food allergy.<sup>44–46</sup> The Learning Early About Peanut (LEAP) trial, a landmark RCT, showed that in high-risk infants (defined as those with severe eczema and/or egg allergy), early introduction of PN between 4 and 11 months of age resulted in a significant reduction in PN allergy. The relative risk reduction was 81% at 5 years of age.<sup>47</sup> The Persistence of Oral Tolerance to Peanut (LEAP-On) follow-up study investigated whether the rate of PN allergy in participants who had consumed PN in the primary trial would remain low after 12 months of PN avoidance.<sup>48</sup> It showed that the benefits of early PN introduction persisted after a 12-month period of PN avoidance. Based on these findings, the American Academy of Pediatrics has endorsed the updated guidelines regarding high-risk infants (severe eczema and/or egg allergy) and have recommended early introduction of PN between 4 and 6 months of age, with PN IgE testing prior to introduction. In these high-risk infants, if a serum-specific IgE is used to screen and is positive (PN sIgE  $\geq 0.35$  kU/L), referral to an allergy specialist for PN SPT and possible supervised feeding are advised. If SPTs are used to screen, results of 0–2 mm have a 95% NPV and home or office introduction is recommended. A 3–7 mm positive skin test has a moderate to high risk and supervised

office introduction or graded oral challenge is recommended. Finally, if the SPT is >8 mm, they are likely allergic and should be referred to an allergy specialist. Those at a lower risk (mild to moderate eczema) are recommended to introduce PN at ~6 months taking into account family/cultural preferences. In addition, low-risk (no eczema or food allergy) infants should introduce PN with other solids according to family/cultural preferences.<sup>49</sup>

Application of these findings remains uncertain as there is no universal agreement on the definition of high-risk infants.<sup>50</sup> It is also not clear if these positive outcomes can be generalized to the general population who are not necessarily at high risk.<sup>51</sup>

The Enquiring about Tolerance (EAT) trial examined whether early introduction of six allergenic food items (PN, egg, CM, sesame, whitefish, and wheat) in exclusively breastfed infants would reduce the prevalence of food allergy by the age of 3 years. In the treatment group, food items were introduced at 3 months of age and continued until 1 year when they were compared to infants who were exclusively breastfed for 6 months (standard introduction group).<sup>52</sup> The intention-to-treat analysis revealed a 20% reduction in the prevalence of food allergy in the early introduction group, not statistically significant, but likely related to the high rate of nonadherence to the dietary protocol; the per protocol analysis showed a significant difference.

The Hen's Egg Allergy Prevention (HEAP) study (randomized, placebo-controlled trial) evaluated the efficacy and safety of early hen's egg introduction at age 4–6 months to prevent hen's egg allergy in the general population. Of 406 children screened, 383 non-sensitized infants were randomized to receive either verum (egg white powder) or placebo (rice powder). The study in contrast found no evidence that consumption of hen's egg starting at 4–6 months of age prevented hen's egg sensitization or allergy.<sup>53</sup>

## Eczema prevention

A personal history of eczema is one of the strongest risk factors for food allergy. In a study by Martin et al, one in five infants with eczema had challenge-confirmed allergy to egg white, PN, or sesame by 12 months of age, compared with only one in 25 infants without eczema. In addition, those with earlier age of onset eczema (first 3 months of life) and increasing severity of eczema (based on treatment required for control) were more likely to develop a food allergy.<sup>54</sup>

Skin barrier dysfunction is a feature of eczema and is thought to play an important role in allergic sensitization and subsequent progression to food allergy and other allergic



disease.<sup>55,56</sup> Therefore, prevention of eczema in early life may prevent development of future food allergy and other allergic diseases. One of the primary targets for eczema prevention is improving skin barrier integrity through regular application of a moisturizing cream in infants. An RCT supported the efficacy of this intervention for reducing eczema with significant relative risk reductions ranging from 32% to 50%. However, it is yet to be determined whether prevention of eczema in early life will subsequently prevent allergic sensitization and food allergy.<sup>57,58</sup>

## Summary

Anaphylaxis is an acute and potentially life-threatening allergic reaction. There are a variety of causes; however, food allergy continues to be the leading cause of anaphylaxis and the predominant cause in children. Early recognition and subsequent treatment with epinephrine are critical. Although current management still advises strict avoidance of some foods, new advances in treatment are on the horizon, most notably in the area of PN desensitization. New recommendations for primary prevention of PN and possibly other food allergens will hopefully disrupt the rising prevalence of this important clinical problem.

## Study limitations

The literature review did not limit our search to study designs engineered to assess the best quality of evidence. Our broad objective was to highlight current evidence on food allergy and anaphylaxis. In addition, we did not address potential sources of variability between the studies by conducting quality assessment and critical appraisal.

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## References

1. Sampson HA, Munoz-Furlon A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – second national institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. *J Allergy Clin Immunol.* 2006;117(2):391–397.
2. LoVerde D, Onyinye II, Eginli A, Krishnaswamy G. Anaphylaxis. *Chest.* 2017;153(2):528–543.
3. Simons FER, Arduzzo LRF, Bilo B, et al; World Allergy Organization. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J.* 2011;4:13–37.
4. Lee S, Hess EP, Lohse C, Gilani W, Chamberlain AM, Campbell RL. Trends, characteristics, and incidence of anaphylaxis in 2001–2010: a population-based study. *J Allergy Clin Immunol.* 2017;139(1):182–188.
5. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* 2010;126(3):477–480.
6. Gonzalez-Estrada A, Silvers SK, Klein A, Zell K, Wang XF, Lang DM. Epidemiology of anaphylaxis at a tertiary care center: a report of 730 cases. *Ann Allergy Asthma Immunol.* 2017;118(1):80–85.
7. Soller L, Shoshan BM, Harrington DW, et al. Prevalence and predictors of food allergy in Canada: a focus on vulnerable populations. *J Allergy Clin Immunol Pract.* 2015;3(1):42–49.
8. Acker WW, Plasek JM, Blumenthal KG, et al. Prevalence of food allergies and intolerances documented in electronic health records. *J Allergy Clin Immunol.* 2017;140(6):1587–1591.
9. Leickly FE, Kloepfer KM, Slaven JE, Vitalpur G. Peanut allergy: an epidemiologic analysis of a large database. *J Pediatr.* 2018;192:223–228. e1.
10. O’Keefe A, Clarke A, St Pierre Y, et al. The risk of recurrent anaphylaxis. *J Pediatr.* 2017;180:217–221.
11. Muñoz-Cano R, Pascal M, Araujo G, et al. Mechanisms, cofactors, and augmenting factors involving in anaphylaxis. *Front Immunol.* 2017;8:1193.
12. Simons FER, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: world allergy organization anaphylaxis guidelines. *World Allergy Organ J.* 2015;8(32):1–16.
13. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol.* 2010;125(2 suppl 2):S116–S125.
14. Lee S, Bellolio MF, Hess EP, Erwin P, Murad MH, Campbell RL. Time of onset and predictors of biphasic anaphylactic reactions: a systematic review and meta-analysis. *J Allergy Clin Immunol.* 2015;3(3):408–416. e1–2.
15. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis – a practice parameter update. *Ann Allergy Asthma Immunol.* 2015;115(5):341–384.
16. Simons FER. Anaphylaxis. *J Allergy Clin Immunol.* 2010;125(2):163–181.
17. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test – European standards. *Clin Transl Allergy.* 2013;3(1):3.
18. Griffiths RLM, El-Shanawany T, Jolles SRA, et al. Comparison of the performance of skin prick, immunoCAP and ISAC tests in the diagnosis of patients with allergy. *Int Arch Allergy Immunol.* 2017;172(4):215–223.
19. Fishbein AB, Makhija MM, Pongracic JA. Anaphylaxis to food. *Immunol Allergy Clin N Am.* 2015;35(2):231–245.
20. Klemans RJ, van Os-Medendorp H, Blankestijn M, Bruijnzeel-Koomen CA, Knol EF, Knulst AC. Diagnostic accuracy of specific IgE to components in diagnosing peanut allergy: a systematic review. *Clin Exp Allergy.* 2015;45(4):720–730.
21. Tuano K, Davis CM. Utility of component-resolved diagnostics in food allergy. *Curr Allergy Asthma Rep.* 2015;15(6):32.
22. Akuete K, Guffey D, Israelsen RB, et al. Multicenter prevalence of anaphylaxis in clinic-based oral food challenges. *Ann Allergy Asthma Immunol.* 2017;119(4):339–348. e1.
23. Chan JC, Peters RL, Koplin JJ, et al. Food challenge and community-reported reaction profiles in food-allergic children aged 1 and 4 years: a population-based study. *J Allergy Clin Immunol Pract.* 2017;5(2):398–409. e3.
24. Yanagida N, Sato S, Asaumi T, Ogura K, Ebisawa M. Risk factors for severe reactions during double-blind placebo-controlled food challenges. *Int Arch Allergy Immunol.* 2017;172(3):173–182.
25. Sheikh A, Simons FE, Barbour V, Worth A. Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community. *Cochrane Database Syst Rev.* 2012;8:CD008935.

26. EpiPen® (Sterile epinephrine injection) USP Unidose 0.3 mg epinephrine auto-injector [Prescribing Information]. CA, USA: Dey Pharma, L.P. Napa; 2012.
27. EpiPen® Jr. (Sterile epinephrine injection) USP Unidose 0.15 mg epinephrine auto-injector [Prescribing Information]. CA, USA: Dey Pharma, L.P. Napa; 2012.
28. Sicherer SH, Simons FER; Section on Allergy and Immunology. Epinephrine for first-aid management of anaphylaxis. *Pediatrics*. 2017;139(3):e20164006.
29. Cheng A. Emergency treatment of anaphylaxis in infants and children. *Paediatr Child Health*. 2011;16(1):35–40.
30. Cantrell FL, Cantrell P, Wen A, Gerona R. Epinephrine concentrations in EpiPens after the expiration date. *Ann Intern Med*. 2017;166(12):918–919.
31. Hogue SL, Goss D, Hollis K, Silvia S, White MV. Training and administration of epinephrine auto-injectors for anaphylaxis treatment in US schools: results from the EpiPen4Schools pilot survey. *J Asthma Allergy*. 2016;9:109–115.
32. White MV, Hogue SL, Bennett ME, et al. EpiPen4Schools pilot survey: occurrence of anaphylaxis, triggers, and epinephrine administration in a U.S. school setting. *Allergy Asthma Proc*. 2015;36(4):306–312.
33. Feuille E, Lawrence C, Volel C, Sicherer SH, Wang J. Time trends in food allergy diagnoses, epinephrine orders, and epinephrine administrations in New York City schools. *J Pediatr*. 2017;190:93–99.
34. Waserman S. Global review of epinephrine availability and anaphylaxis management practices amongst patient organization countries. Abstracts from the European Academy of Allergy and Clinical Immunology Congress; June 17–21; 2017; Helsinki, Finland; 72 (S103):216–217.
35. Waserman S, Chad Z, Francoeur MJ, et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. *Allergy*. 2010;65(9):1082–1092.
36. Leonard SA, Sampson HA, Sicherer SH, et al. Dietary baked egg accelerates resolution of egg allergy in children. *J Allergy Clin Immunol*. 2012;130(2):473–480.
37. Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol*. 2011;128(1):125–131.
38. Gernez Y, Nowak-Węgrzyn A. Immunotherapy for food allergy: are we there yet? *J Allergy Clin Immunol Pract*. 2017;5(2):250–272.
39. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol*. 2017;139(1):173–181.e8.
40. Bird JA, Spergel JM, Jones SM, et al; ARC001 Study Group. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. *J Allergy Clin Immunol Pract*. 2018;6(2):476–485.e3.
41. Jones SM, Sicherer SH, Burks AW, et al; Consortium of Food Allergy Research. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. *J Allergy Clin Immunol*. 2017;139(4):1242–1252.e9.
42. Shreffler WG. Efficacy and safety of long-term epicutaneous immunotherapy (EPIT) treatment of peanut allergy with Viaskin® peanut: results of the two-year extension of the VIPES phase IIb clinical trial. Presented at: Annual Meeting of the American Academy of Allergy, Asthma & Immunology; March 5; 2017; Atlanta, GA.
43. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 suppl):S1–S58.
44. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol*. 2008;122(5):984–991.
45. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol*. 2010;126(4):807–813.
46. Katz Y, Rajuan N, Goldberg MR, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol*. 2010;126(1):77–82.e1.
47. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803–813.
48. Du Toit G, Sayre PH, Roberts G, et al. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med*. 2016;374(15):1435–1443.
49. Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: report of the national institute of allergy and infectious diseases-sponsored expert panel. *Ann Allergy Asthma Immunol*. 2017;118(2):166–173.
50. Hoffman B, Moreno L, Gerber L, D'Angelo E, Abramson E. What pediatricians are advising on infant peanut introduction. *Ann Allergy Asthma Immunol*. 2017;119(5):S10.
51. Fleischer DM. Life after LEAP: how to implement advice on introducing peanuts in early infancy. *J Paediatr Child Health*. 2017;53(S1):3–9.
52. Perkin MR, Logan K, Tseng A, et al. Randomized trial of introduction of allergenic foods in breast-fed infants. *N Engl J Med*. 2016;374(18):1733–1743.
53. Bellach J, Schwarz V, Ahrens B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol*. 2017;139(5):1591–1599.e2.
54. Martin PE, Eckert JK, Koplin JJ, et al; HealthNuts Study Investigators. Which infants with eczema are at risk of food allergy? Results from a population-based cohort. *Clin Exp Allergy*. 2015;45(1):255–264.
55. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol*. 2008;121(6):1331–1336.
56. Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol*. 2017;139(6):1723–1734.
57. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):824–830.e6.
58. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818–823.

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